The Effect of Cardiac Troponin Testing on Clinical Care in a Veterans Population

A Randomized Controlled Trial

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BACKGROUND: Cardiac troponin is more accurate than creatine kinase (CK) testing for detecting myocardial injury in patients with acute coronary syndromes (ACS), but its effects on clinical care compared with CK testing alone is open to question.

OBJECTIVE: To test the effects of troponin I on medical decisions for patients undergoing cardiac enzyme testing.

DESIGN: Randomized, controlled trial.

SETTING: Urban academic Veterans Affairs medical center.

PATIENTS: Three hundred ninety-two patients presenting to the emergency department (ED) and outpatient settings with symptoms and/or electrocardiograms suggestive but not diagnostic of ACS.

INTERVENTION: Random assignment to linked CK-troponin I (CKTnI) testing or CK testing alone.

MEASUREMENTS: ED discharge and cardiac catheterization incidence (primary); ED medication use, inpatient noninvasive testing, revascularization procedures, discharge medications, and 8-week ED visits, hospitalizations, and procedures (secondary).

RESULTS: Groups were similar in all variables except history of heart failure (CK 26.8% vs CKTnI 17.0%). ACS comprised 12.2% of the cohort. ED discharge incidence was greater in the CKTnI arm (18% vs 9.6%; relative risk [RR], 1.83; 95% CI, 1.08 to 3.31; P=.02; number needed to test=12.6; 95% CI, 4.5 to 130). Troponin testing had no significant effect on catheterization incidence (18.2% vs 14.5%; RR, 1.19; 95% CI, 0.72 to 1.92; P>.20) or other outcomes except follow-up echocardiography (13.4% vs 7.4%; RR, 2.24; 95% CI, 1.11 to 4.69; P=.02).

CONCLUSIONS: In a veterans population undergoing cardiac enzyme testing, CKTnI testing led to more ED discharges than CK testing alone but had no effect on inpatient care and was associated with more echocardiograms in a follow-up period.

KEY WORDS: troponin; cardiac enzymes; cardiovascular diseases; acute coronary syndromes; chest pain.
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Serum cardiac troponin testing has become the standard of care for detecting myocardial injury and stratifying risk in patients with unstable angina and acute myocardial infarction (acute coronary syndromes; ACS),[1–6] and one widely accepted set of guidelines suggests it should replace creatine kinase (CK) testing altogether in this population.[7] Because of its superior performance in ACS patients, troponin testing has been widely adopted for first-line use in all patients undergoing cardiac enzyme testing, including those with and without ACS presenting at different times after symptom onset with and without classic symptoms and diagnostic electrocardiograms (ECGs). The evidence supporting this practice largely comes from observational studies demonstrating that troponin improves diagnostic and prognostic accuracy in patients with chest pain when measured simultaneously with other cardiac markers.[8,9] However, systematic reviews of troponin testing in emergency departments (ED) have documented the many gaps in evidence supporting more general use of the test, including a relative lack of evaluation in a wide patient spectrum and the absence of studies demonstrating its effects on decisions and outcomes compared to other markers.[10,11] Decision and cost-effectiveness models have suggested the test is best reserved as a secondary diagnostic measure,[12,13] and 2 randomized controlled trials comparing linked CK-and-troponin testing to CK testing alone differed in their conclusions regarding the added value of troponin.[14,15]

Troponin's test characteristics nevertheless make it attractive in principle as a first-line test for use in at least some patient populations who undergo cardiac enzyme testing.[16] Veterans are one such population. They have a high prevalence of coronary risk factors and frequent visits for symptoms suggestive of ACS. They have comorbidities and exposures, such as renal insufficiency and cocaine use, that contribute to both heart disease and CK elevations and render CK testing alone less useful for diagnosis. And they often present belatedly for evaluation when measurement of troponin, which stays elevated 72 hours or longer after the onset of myocardial injury, would have particular utility.

For these reasons, we thought cardiac troponin testing might be especially useful in a veterans population, and sought to compare the effects of troponin and CK testing on clinical care in the ED and inpatient setting of a veterans hospital. We hypothesized that the addition of troponin I to CK and CK-MB testing would increase discharges from the ED of patients at low risk for ACS, and would increase the proportion of diagnostic catheterizations of patients admitted for evaluation by detecting ACS missed by CK testing alone.

METHODS

Study Design

The study was a randomized controlled trial conducted at a 150-bed urban VA medical center in the mid-Atlantic United States before troponin testing was routinely available for use by providers. Patients with symptoms prompting providers to order cardiac enzyme (CK/CK-MB) testing in the medical center's ED or other outpatient settings were randomly assigned to undergo CK/CK-MB and troponin I testing, or CK/CK-MB testing alone. Patients were enrolled between July 1999 and

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November 2000. Analyses include all endpoints occurring between July 1999 and January 2001.

Study Population

All patients presenting for care with symptoms prompting cardiac enzyme testing in the medical center's ED or other outpatient settings were eligible for study inclusion. Patients were excluded if they had: 1) diagnostic ECGs (defined as pathologic Q waves, ST-segment elevations ≥ 2 mm, ST-segment depressions ≥ 1 mm, or bundle-branch blocks, any of which were thought to be acute and ischemic in origin); 2) acute or suspected acute dysrhythmias (including syncope or suspected implantable cardioverter defibrillator [ICD] or pacemaker malfunction); 3) primary noncardiac reasons for ACS (such as gastrointestinal hemorrhage) or admission (such as stroke) in which acute ACS, if suspected, was thought to be a secondary process; or 4) enzymes drawn to evaluate peripheral muscle disorders. Patients with diagnostic ECGs were excluded on the premise that cardiac marker testing would be expected to have little effect on triage and catheterization decisions after ACS was identified; patients with acute or suspected acute dysrhythmias were excluded on the premise that few would be discharged home and most were likely to undergo procedures (such as electrophysiologic testing) and treatments (such antiarrhythmic drug therapy) different from patients with suspected ACS. Patients were also excluded if they refused or were unable to give consent, if they were previously enrolled in the study, and for miscellaneous reasons (such as the immediate transfer of nonveterans to private hospitals, patients cared for by a study investigator, and eligible patients misclassified as ineligible for study inclusion). Eligible consecutive patients were enrolled 24 hours a day, 7 days a week, until the predetermined sample size was reached.

Randomization

The study's allocation schedule was generated by study investigators using the RANNOR random number generator in SAS version 6.12 (SAS Institute, Cary, NC). Anticipating differences in ED provider decisions based on perceptions of likelihood of disease, we initially stratified allocation into low- ($<10\%$), intermediate- (10%–55%), and high- ($>55\%$) probability populations based on providers' quantitative pretest estimates of the probabilities of ACS. Patients were then randomized within stratum and within ED provider in blocks of 4. Clinicians were masked to the stratification thresholds and allocation schedule throughout the study, and the individual assigning patients was masked to clinical details except those necessary to determine patient eligibility. Allocation was centralized and revealed only at the time of patient assignment.

Study Protocol and Intervention

Quantitative CK and troponin I testing were performed in the central hospital laboratory on all study patients. Laboratory personnel contacted a study coordinator upon receipt of specimens, and the coordinator then ascertained patient eligibility and estimated probability of ACS from ED providers by telephone or in person. Patients meeting inclusion criteria and granting written informed consent were enrolled and randomized to receive CK with troponin I (CKTnI) or CK testing alone by the study coordinator. The term CK testing is used in this paper to designate CK and CK-MB testing because by standard laboratory protocol, MB mass was automatically performed for CK values ≥ 150 IU/L. All patients underwent both CK and troponin I testing regardless of allocation, but those randomized to CKTnI had both results and those undergoing CK testing alone had only CK results released to providers by standard protocol (i.e., via the hospital computer information system). Both initial enzymes and serial enzymes ordered up to 24 hours after initial testing (if patients were hospitalized or had prolonged ED stays) were included in study analyses. Only CK information was released on serial specimens for CK-only patients; CKTnI patients reverted to CK-only status after 24 hours per standard hospital practice. Information on outcomes was obtained by daily chart review and by a 60-day follow-up interview by telephone or in person. Missing data were obtained by patient record review.

All physicians, nurse practitioners, and physician assistants working in the ED and inpatient units during the study period participated and were masked to study hypotheses; ED providers were masked to outcomes. No established protocols or guidelines existed to guide provider decisions; standard ED practice prior to the study was to admit all patients undergoing enzyme testing to inpatient settings for at least 18 hours at the time studies were first ordered, but providers were free during the investigation to discharge patients to home or hospital with single or multiple enzyme measurements with or without troponin information as they saw fit.

Laboratory Assays

CK and MB mass were measured on an Axsym analyzer (Abbott Laboratories, Abbott Park, IL). CK relative indices were calculated by dividing the MB mass by the total CK and multiplying by 100. Troponin I specimens were also run on an Abbott Axsym analyzer (a first-generation troponin assay) until manufacturer supply difficulties mandated a transfer of testing platforms to a Beckman Access analyzer (a second-generation troponin assay; Beckman Instruments, Chaska, MN) in August 2000.[17] Providers were informed of a change in troponin reference ranges at the time of the transfer but were masked to the reasons for the change. Nonelevated and elevated values were distinguished by biochemical (not clinical) criteria defined by assay manufacturers and detailed in the Appendix (available online).

Outcomes

Primary outcomes were early events, and secondary outcomes were both early and delayed events. There were no composite outcomes. Primary outcomes included ED discharge and in-hospital cardiac catheterization (for patients who were admitted). Patients designated as leaving the ED "against medical advice" were considered hospitalized. The hospital had no formal chest pain observation unit, and patients kept in the ED for overnight observation due to lack of inpatient hospital beds were also considered hospitalized. Cardiac catheterization was chosen as a primary outcome because it is a frequent clinical event and is an intermediate step between diagnostic testing and interventions proven to reduce morbidity and mortality.

Early secondary outcomes included ED medication use; inpatient use of imaging studies and revascularization procedures; inpatient lengths of stay; hospital discharge medica-

tions; and deaths. Delayed secondary outcomes comprised events occurring in a 60-day period following the patient's index ED visit, and included recurrent ED visits and hospitalizations for cardiovascular symptoms or diagnoses; invasive and noninvasive cardiovascular testing; medication use; and deaths. Follow-up use of health resources was ascertained by patient interviews and confirmed by VA electronic medical record review, including pharmacy database review for medication data. Follow-up use of non-VA resources was confirmed by medical record documentation from outside providers and facilities. Follow-up was considered "partial" when information on VA resource use was available but reported non-VA resource use could not be confirmed; when patients could not be contacted for interviews but had documentation of VA medical visits in the follow-up period; or when follow-up information existed for ≤ 30 days of the 60-day follow-up period. All available data from patients with partial follow-up were included in study analyses.

Study personnel were not masked to cardiac enzyme results during assessment of primary and secondary early outcomes, but outcome assessments relied on documents (such as discharge instructions and catheterization reports) completed by clinical providers masked to study hypotheses. Study personnel were masked to cardiac enzyme results during assessment of secondary delayed outcomes.

All discharge diagnoses, including that of acute myocardial infarction, were determined clinically by inpatient physicians based on all clinical information available to them, including but not limited to history and physical examination, ECG, cardiac biomarkers, noninvasive and invasive testing, and the patient's clinical course.

Statistical Analysis

The study was designed to have 80% power to detect a 15% absolute difference in catheterization rates among patients thought to be at intermediate risk of ACS, based on a review of data suggesting a baseline incidence of CK elevation of 20% among ED patients evaluated for cardiac symptoms; CK data were used because medical record systems did not allow identification of the subset of patients undergoing catheterization who were hospitalized from the ED. Discordance of CK and troponin testing was tested using McNemar's test for binomial proportions for matched-pair data. Relative risk of ED outcomes was estimated from the odds ratio and baseline risk of logistic regression, where baseline risk represented the risk of outcomes for patients without history of heart failure undergoing CK testing alone. Confidence intervals for the relative risk were estimated by nonparametric bootstrap resampling of the logistic regression. Bootstrap resampling was performed at the ED provider level to account for possible clustering of patient outcomes within ED provider. Regression analyses of ED outcomes included variables for study assignment, patient history of heart failure (because of the significant baseline difference between groups in this variable), and provider (all categorical variables). Relative risk of inpatient outcomes was estimated similarly, though there was no clustering of patients by provider in the inpatient setting, and provider was therefore not adjusted for in analyses. Estimates of number needed to test (NNT) were estimated from the baseline event risk in the CK group and the adjusted event risk in the CKTnI group was computed from the adjusted relative risk. Confidence intervals for the NNT were estimated from the same baseline and adjusted relative risk. Relative risk and incidence rate ratios based on 60 days of follow-up were calculated using logistic and Poisson regression analysis, respectively, adjusting for study assignment, ED discharge, and baseline differences (each categorical), where baseline incidence represented incidence of outcome for hospitalized patients without history of heart failure undergoing CK testing alone. In a decision made after patient enrollment but prior to data analysis, patients were pooled from pretest probability randomization strata because small patient numbers in the low- and high-probability strata precluded meaningful analyses by stratum. All analyses were intention-to-test and were performed using Stata version 6.0 (Stata Corporation, College Station, TX).

Funding and Review

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RESULTS

The trial profile is detailed in Figure 1 and characteristics of the 392 participants are detailed in Table 1. Patients undergoing CK testing alone were more likely to have a history of heart failure but subjects were otherwise not statistically significantly different. Overall incidence of renal insufficiency was 15.3%; overall incidence of cocaine use was 11.5%. Median time of presentation after symptom onset was 24 hours for the cohort (interquartile range, 4 to 96). Eleven pa-

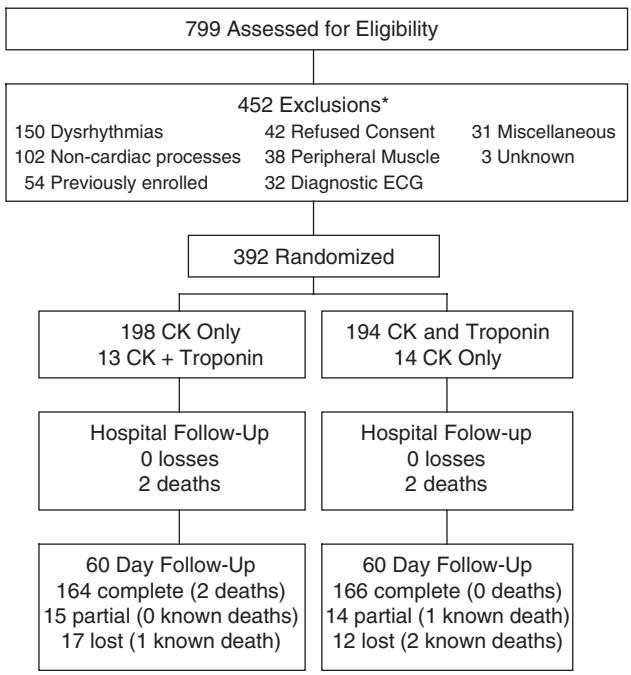

FIGURE 1. Trial profile. *Forty-five patients excluded for 2 reasons.

Table 1. Baseline Characteristics of the 392 Study Participants

Characteristic	CK (*n*=198)	CKTnI (*n*=194)	*P* Value
Median age, y (range)	62 (30–90)	57 (25–89)	.32
Sex, *n* (%)			
Male	192 (97.0)	185 (95.4)	.41
Female	6 (3.0)	9 (4.6)	
Race,* *n* (%)			
Black	118 (61.8)	129 (67.2)	.43
White	65 (34.0)	53 (27.6)	
Hispanic	8 (4.2)	9 (4.7)	
Other	0 (0.0)	1 (0.5)	
Coronary risk factors†			
Risk factors, median (range)	2 (0–4)	2 (0–4)	.43
Hypertension, *n* (%)	143 (72.2)	148 (76.3)	.36
Tobacco, *n* (%)			.25
Current	91 (47.6)	75 (39.3)	
Former	68 (35.6)	77 (40.3)	
Never	32 (16.8)	39 (20.4)	
Diabetes mellitus, *n* (%)	63 (31.8)	71 (36.6)	.32
Hyperlipidemia, *n* (%)	70 (35.4)	80 (41.2)	.23
Coronary and AS history			
Prior CAD, *n* (%)	106 (53.5)	111 (57.2)	.46
Coronary procedures, *n* (%)	41 (20.7)	38 (19.6)	.78
CVA, *n* (%)	27 (13.6)	30 (15.5)	.61
PAD, *n* (%)	14 (7.1)	22 (11.3)	.14
Heart failure	53 (26.8)	33 (17.0)	.02
Medications, *n* (%)			
Aspirin	99 (50.0)	115 (59.3)	.07
Beta-blockers	63 (35.1)	68 (31.8)	.50
ACE inhibitors	70 (35.4)	65 (33.5)	.70
Nitrates	73 (36.9)	67 (34.5)	.63
Diuretics	77 (38.9)	75 (38.7)	.96
CA-channel blockers	50 (25.3)	57 (29.4)	.36
Lipid-lowering agents	54 (27.3)	57 (29.4)	.64
Comorbidities			
Pulmonary disease, *n* (%)	34 (17.2)	35 (18.0)	.82
Renal insufficiency, *n* (%)	31 (15.7)	29 (14.9)	.85
Cocaine use			.60
Current	24 (12.1)	21 (10.8)	
Former	18 (9.1)	13 (6.7)	
Vital signs, median (range)			
SBP	140 (64–238)	141 (75–218)	.61
DBP	78 (36–154)	80 (15–148)	.95
HR	83.5 (22–170)	78 (18–145)	.06
RR	20 (12–85)	18 (12–68)	.77
ECG findings (2 or more contiguous leads, *n* (%)			
T wave inversions or pseudonormalization	66 (33.7)	65 (33.5)	.97
Nonspecific ST-segment changes	40 (20.4)	31 (16.0)	.26
LVH/repolarization	21 (10.7)	29 (14.9)	.21
Bundle-branch block	21 (10.7)	24 (12.4)	.61
ST-segment depressions <1 mm	15 (7.7)	15 (7.7)	.98
Poor R-wave progression	12 (6.2)	12 (6.1)	.98
Old infarction	5 (2.6)	10 (5.2)	.18
Primary presenting symptom, *n* (%)			
Chest pain or equivalent	152 (76.8)	156 (80.4)	.66
Dyspnea	34 (17.2)	29 (15.0)	
Other‡	12 (6.1)	9 (4.6)	
Time from symptom onset (median hours [IQR])	21 [4, 96]	24 [3, 72]	.21

**Data missing for 9 patients (7 CK, 2 CKTnI).*

†Risk factors: hypertension, diabetes mellitus, hyperlipidemia, and tobacco use.

‡Other symptoms: abdominal pain, diaphoresis, dizziness, fatigue or weakness, incidental ECG findings, lower extremity edema, mental status changes, nausea and vomiting, palpitations.

CK, creatine kinase; CKTnI, CK and troponin I; AS, atherosclerosis; CAD, coronary artery disease; CVA, cerebrovascular accident; PAD, peripheral arterial disease; ACE, angiotensin converting enzyme; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; RR, respiratory rate; ECG, electrocardiogram; LVH, left ventricular hypertrophy; IQR, interquartile range.

tients (6 in the CK, 5 in the CK-TnI arm) left the ED against medical advice. Study patients were evaluated and enrolled by 35 ED providers, including 3 general internists (177 patients, range 33–77), 21 internal medicine–trained fellows at post-graduate year 4 level of training or higher (112 patients, range 1–12), 1 physician assistant (83 patients), one family practice–trained, ED-boarded physician (18 patients), and 1 nurse practitioner (8 patients); 8 providers were excluded from study

Table 2. Distribution of Lab Values*

	CK (IU/L) (*n*=392)	MB† (ng/dL) (*n*=197)	RI† (MB %) (*n*=197)	Troponin I (ng/mL)	
				All Patients‡ (*N*=392)	CKTnI Only (*n*=194)
Initial, median (range)	152 (11–4488)	3.2 (0.6–77.3)	1.2 (0.1–12.3)	0.0 (0–202)§ 0.0 (0–5.7)‖	0.0 (0–202)§ 0.0 (0–0.13)‖
Peak, median (range)	158.5 (12–4488)	3.3 (0.5–177.7)	1.4 (0.1–22.4)	0.3 (0–202)§ 0.03 (0–5.7)‖	0.4 (0–202)§ 0.03 (0–0.76)‖
Patients with elevation, *n* (%)					
Initial					
Any	–	–	NA	132 (34.8)	66 (34.0)
AMI criteria	–	–	30 (7.7)¶	12 (3.2)	5 (2.6)
Peak					
Any	–	–	NA	184 (46.9)	91 (46.9)
AMI criteria	–	–	35 (8.9)¶	30 (7.7)	13 (6.7)

*See online-only Appendix for definitions of normal and abnormal values.
†Data for patients with CK elevations (CK > 150 IU/L) only.
‡Data include both unmasked troponin results from CKTnI arm and masked troponin results from CK-only arm.
§Abbott Axsym troponin assay (298 patients).
‖Beckman Access troponin assay (94 patients).
¶AMI criteria for CK: RI > 2.5 when MB mass > 3.8 and CK ≥ 150; %=percentage of all participants (N=392).
CK, creatine kinase; RI, relative index; TnI, troponin I; AMI, acute myocardial infarction; NA, not applicable.

analyses because they did not enroll at least 1 patient in both study arms and thus provided no meaningful information in analyses by study assignment. Regression analyses of ED outcomes with and without stratification by provider were equivalent, ruling out confounding by provider.

Laboratory Data

A mean of 2.66 (± SD, 0.94; range 1–5) serial enzyme tests per patient were ordered to evaluate symptoms. Lab results are presented in Table 2. The median initial and peak serial value for CK and troponin in the study were negative or borderline negative. Only 30 patients, or 7.7%, had abnormal CKs with elevated relative indices on presentation, and only 5 additional patients had CK with MB and relative index elevations on subsequent serial testing. By contrast, 66 patients, or 34.0%, had troponin I elevations at presentation, and an additional 25 (91 total patients, or 46.9%) had abnormal troponin values on subsequent testing. Only 13 (6.7%) had any elevation to acute myocardial infarction (AMI) levels as defined by assay manufacturers (See Appendix, available online). These percentages were similar when troponin values performed but not released for the CK-only arm were included in analyses. CK testing appeared to detect more myocardial infarctions than troponin testing, but only 11 patients in this group were given the clinical diagnosis of ACS (2.8% of all enrolled patients, 22.9% of patients with ACS).

Mild (non-AMI) troponin I elevations accompanied normal CK values in about one third of patients; significantly more patients had troponin I elevations with normal CK levels than had CK elevations with normal troponin I levels (see Tables 3A1–3B2; $P<.001$ for all groups). Of the 7 CKTnI patients who had elevated peak CKs with normal troponin values (Table 3A2), 2 had normal CKs that were nevertheless above the laboratory threshold for measuring CK-MB mass, 3 had modest CK elevations (between 220 and 370 IU/L) not thought to be cardiac in origin, and 2 had substantial elevations (>800 IU/L) following cocaine and alcohol exposures. None was given the diagnosis of ACS. Of the additional 7 patients in the CK arm who had elevated peak CKs but whose normal troponin values were not released to providers (Table 3B2), 4 had normal CKs that were nevertheless above the laboratory threshold for measuring MB mass, 1 had a modest CK elevation (CK=203 IU/L) in the presence of heart failure, 1 had a more substantial elevation (CK=475) thought by inpatient providers to be ischemic and by outpatient attendings to be nonischemic in origin, and 1 had a modest elevation (CK=239) accompanying non-ST-segment-elevation myocardial infarction.

Clinical Spectrum

Clinical discharge diagnoses (those given on discharge from the ED or inpatient setting and incorporating but not based exclusively on laboratory data) are detailed in Table 4. Just over half of all patients were given the nonspecific diagnosis of "chest pain" or "chest pain, rule out myocardial infarction." "Heart failure" was the second most common diagnosis, occurring in 15% of all participants, followed by unstable angina and myocardial infarction, diagnosed in 12% overall. The remaining patients had a variety of other diagnoses related to cardiovascular, pulmonary, and noncardiac systems. There were no differences in any category of diagnosis by study arm.

Outcomes

ED outcomes are listed in Table 5. A majority of patients (86%) were hospitalized, but CKTnI testing led to significantly more ED discharges than CK testing alone (adjusted relative risk for discharge with troponin, 1.83; 95% CI, 1.08 to 3.31; $P=.02$; number needed to test=12.6; 95% CI, 4.5 to 130). Troponin testing had no apparent effect on other ED decisions. Patients in each study arm received equal proportions of cardiac and noncardiac medications, including aspirin and beta-blockers, except those with histories of heart failure were more likely to receive diuretics and less likely to receive aspirin and nitrates acutely (data not shown). In subgroup analyses,

Table 3. Comparison of CK and Troponin I Data in CKTnI (n=194) and All Patients (N=379)*†‡

A1. Initial CK-Troponin Values (n (%)): CKTnI Only				
	Troponin			
	–	+	++	
CK				
Negative	108 (56.8)	63 (33.2)	3 (1.6)	174
Positive	9 (4.7)	5 (2.6)	2 (1.1)	16
	117	68	5	190§
A2. Peak CK-Troponin Values (n (%)): CKTnI Only				
	Troponin			
	–	+	++	
CK				
Negative	96 (50.0)	71 (36.6)	9 (4.6)	176
Positive	7 (4.1)	7 (3.6)	4 (2.1)	18
	103	78	13	194
B1. Initial CK-Troponin (n (%)): All Patients¶				
	Troponin			
	–	+	++	
CK				
Negative	219 (57.8)	126 (33.2)	7 (1.8)	352
Positive	14 (3.7)	8 (2.1)	5 (1.3)	27
	233	134	12	379‖
B2. Peak CK-Troponin Values (n (%)): All Patients¶				
	Troponin			
	–	+	++	
CK				
Negative	194 (49.2)	144 (37.0)	19 (6.1)	357
Positive	14 (3.8)	10 (2.3)	11 (1.5)	35
	208	154	30	392

Criteria for elevation defined by hospital laboratory (CK) and assay manufacturer (troponin I). See online-only Appendix for definitions of cardiac marker elevations.
†*Sum percents may differ slightly from 100 due to rounding.*
‡*P<.001for discordant pairs in all tables.*
§*Four missing values for initial released troponins.*
‖*Thirteen missing values for all initial troponins.*
¶*Includes masked troponin I data from CK-only arm.*
– =negative.
+ =elevated, nonmyocardial infarction.
++ =elevated, acute myocardial infarction.
CK, creatine kinase; CKTnI, CK and troponin I.

all patients with an initially elevated CK relative index were hospitalized, but initial troponin elevations did not independently predict hospitalization, perhaps because only 5 patients in the CKTnI arm had initial troponin values in the AMI range.

Among patients hospitalized for their symptoms, CKTnI testing had no detectable effect on cardiac catheterization, revascularization, diagnostic testing, intensive care unit and hospital lengths-of-stay, discharge medications (except troponin patients were more likely to receive H2-blockers), or inpatient mortality (Table 6). However, in subgroup analyses, elevated peak troponin values were associated with catheterization (OR, 1.75; 95% CI, 0.94 to 3.25; P=.08) and revascularization (OR, 3.0; 95% CI, 1.30 to 6.91; P=.01).

Table 4. Discharge Diagnoses*

Discharge Diagnoses	CK (n=198) (%)	CKTnI (n=194) (%)	Total (N=392) (%)
Chest pain	111 (56.1)	97 (50.5)	208 (53.3)
Heart failure	26 (13.1)	33 (17.2)	58 (15.1)
Acute coronary syndromes	24 (10.1)	24 (14.4)	48 (12.2)
Unstable angina	9 (4.5)	6 (3.1)	15 (3.8)
Myocardial infarction	15 (7.6)	18 (9.3)	33 (8.4)
Pulmonary	6 (3.0)	10 (5.2)	16 (4.1)
Other cardiac	9 (4.5)	6 (3.1)	15 (3.8)
Miscellaneous noncardiac	7 (3.6)	8 (4.0)	15 (3.8)
Gastrointestinal	4 (2.0)	5 (2.6)	9 (2.3)
Neuropsychiatric	4 (2.0)	3 (1.6)	7 (1.8)
Hypertensive urgency	3 (1.5)	2 (1.0)	5 (1.3)
Valvulopathy	4 (2.0)	1 (0.05)	5 (1.3)
Arrhythmias	4 (2.0)	1 (0.05)	5 (1.3)

**Primary discharge diagnosis made by emergency department or inpatient physicians at patient discharge, incorporating but not defined exclusively by laboratory data.*
CK, creatine kinase; CKTnI, CK and troponin I.

Follow-up Outcomes

Sixty-day follow-up was complete for 85% of all patients discharged alive, and complete or partial for 93% (Fig. 1). Eighteen percent had 1 or more repeat ED visits and 16% had 1 or more hospitalizations for acute cardiovascular complaints or conditions following release from their index ED visit and hospitalization. In multivariable analyses (Table 7), neither troponin testing (incidence rate ratio [IRR], 1.54; 95% CI, 0.94 to 2.54; P=.09) nor discharge from the ED (IRR, 1.21; 95% CI, 0.61 to 2.38; P>.20) was associated with subsequent cardiac hospitalization or ED use, but heart failure history was strong-

Table 5. Emergency Department Measures and Outcomes

	CK (n=198) (%)	CK and Troponin I (n=194) (%)	Relative Risk* (95% CI)	P Value
Discharges	19 (9.6)	35 (18.0)	1.83 [1.08 to 3.31]	.02
Medications				
Aspirin	138 (69.7)	135 (69.6)	0.98 [0.90 to 1.10]	>.20
Nitrates	94 (47.7)	90 (46.6)	0.95 [0.84 to 1.23]	>.20
Diuretics	32 (16.2)	31 (16.1)	1.20 [0.77 to 1.90]	>.20
Beta-blockers	30 (15.2)	27 (13.9)	0.90 [0.58 to 2.23]	>.20
Heparin	21 (10.7)	20 (10.4)	0.91 [0.66 to 2.07]	>.20
Morphine sulfate	15 (7.6)	15 (7.8)	0.95 [0.58 to 1.97]	>.20
H2B	8 (4.1)	11 (5.7)	1.31 [0.44 to 3.71]	>.20
Antibiotics	5 (2.5)	5 (2.6)	1.07 [0.34 to 2.08]	>.20
ACE inhibitor	3 (1.5)	3 (1.6)	0.90 [0.24 to 3.49]	>.20
PPI	1 (0.5)	1 (0.5)	0.90 [0.28 to 3.34]	>.20

**Adjusted for heart failure history using logistic regression; relative risks and confidence intervals estimated by nonparametric bootstrap resampling assuming baseline risk for patients without heart failure undergoing CK testing alone. See Methods section for details.*
CK, creatine kinase; H2B, histamine-2 receptor blockers; ACE, angiotensin converting enzyme; PPI, proton pump inhibitor.

Table 6. Inpatient Measures and Outcomes

	CK (n=179) (%)	CK and Troponin I (n=159) (%)	Relative Risk* (95% CI)	P Value
Procedures				
Catheterization	26 (14.5)	29 (18.2)	1.19 [0.72 to 1.92]	>.20
PCI	6 (3.4)	9 (5.7)	1.56 [0.51 to 5.50]	>.20
CABG	2 (1.1)	5 (3.1)	2.72 [0.49 to 9.18]	>.20
PCI or CABG	8 (4.5)	13 (8.8)	1.84 [0.75 to 5.66]	.15
Diagnostic tests				
Echocardiograms	58 (32.4%)	57 (35.8%)	1.12 [0.83 to 1.56]	>.20
Functional studies†	53 (29.6%)	48 (30.2%)	0.99 [0.71 to 1.37]	>.20
Lengths of stay, median (IQR)				
ICU/telemetry	1 [1,3]	2 [1,3]	–	>.20
Hospital	0 [0,2]	0 [0,2]	–	>.20
Total	2 [1,5]	2 [1,5]	–	>.20
Discharge medications, n (%)				
Aspirin	132 (73.7)	111 (69.8)	0.95 [0.83 to 1.10]	>.20
Beta-blockers	85 (47.5)	74 (46.5)	1.00 [0.78 to 1.25]	>.20
Nitrates	67 (37.4)	53 (33.3)	0.93 [0.67 to 1.27]	>.20
Diuretics	82 (45.8)	60 (37.7)	0.87 [0.63 to 1.22]	>.20
ACE inhibitors	76 (42.1)	67 (42.5)	1.06 [0.79 to 1.44]	>.20
CA-channel blockers	37 (20.7)	42 (26.4)	1.36 [0.93 to 2.08]	.14
Lipid-lowering agents	64 (34.0)	54 (35.7)	0.97 [0.71 to 1.31]	>.20
H2-blockers	18 (10.1)	28 (17.6)	1.80 [1.02 to 3.45]	.04
Deaths, n (%)	2 (1.1)	2 (1.2)	1.01 [0.23 to 4.39]	>.20

**Adjusted for heart failure history using logistic regression; relative risks and confidence intervals estimated by nonparametric bootstrap resampling assuming baseline risk for patients without heart failure undergoing CK testing alone. See Methods section for details.*
†Functional studies: exercise treadmill, exercise radionuclide, pharmacologic radionuclide, and pharmacologic echocardiographic testing.
CK, creatine kinase; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; IQR, interquartile range; ICU, intensive care unit; ACE, angiotensin converting enzyme; CA, calcium.

ly predictive of the need for ED (IRR, 2.61; 95% CI, 1.63 to 4.18; P<.001) and inpatient follow-up care (IRR, 3.29; 95% CI, 2.01 to 5.38; P<.001). The marginally significant higher incidence of hospitalization among the troponin group was a partial result of a single troponin-exposed patient hospitalized 4 times after VA discharge for cardiovascular complaints related to cocaine use; removal of this patient from analyses resulted in a nonsignificant estimate (IRR with exclusion, 1.36; 95% CI, 0.82 to 2.27; P>.20). Patients who underwent troponin and CK testing had significantly more echocardiograms in follow-up than those who had CK testing alone, independent of early ED discharge of heart failure. Troponin testing had no other detectable effect on use of cardiac procedures, medication use, or mortality at 8 weeks.

DISCUSSION

A wealth of evidence demonstrates that cardiac troponin is more accurate than creatine kinase testing for detecting myocardial injury and stratifying risk in patients with acute coronary syndromes.[1–6] However, data on troponin's effects on actual clinical care compared to CK testing alone in a heterogeneous patient population (including patients with and without acute cardiac disease presenting at different times in their illnesses with and without classic symptoms and diagnostic ECGs) are limited. In one such population, we found that combined CK and troponin I (CKTnI) testing led to more ED discharges than CK testing alone. We did not detect any difference in adverse events over 60 days as a result of the greater number of ED discharges, though our study was not powered to detect delayed outcomes. CKTnI testing appeared to have little or no effect on inpatient care, including decisions to recommend diagnostic catheterization or revascularization, but was associated with more noninvasive testing in a follow-up period. A subgroup of hospitalized patients with elevated peak troponin levels underwent more revascularization procedures.

Our findings differ from those of two other similar trials reported in the literature. The first, a study of chest pain patients presenting within 12 hours of symptom onset to a Canadian ED, failed to detect any effect of linked myoglobin-CK-troponin I testing over CK testing alone on admission rates and other outcomes.[14] The second trial of linked CK-troponin T testing also did not demonstrate any overall effect of troponin at an ED level but reported a reduction in hospital length of stay and total charges.[15] Limited methodological details in both studies precluded detailed comparison of study designs and full interpretation of results. At least two characteristics of our study population may account for differences in results between these trials and our own. First, despite high prevalences of coronary risk factors, our study cohort was at relatively low risk for ACS, as evidenced by mostly normal or elevated non-AMI troponin levels. Second, patients in the study presented for care unusually late, a median of 24 hours after symptom onset. The high specificity and prolonged elevation of troponin make it an ideal technology for excluding myocardial injury under these conditions.[11]

Troponin testing appeared to have no effect on inpatient resource use or clinical events. While the reasons for this cannot be inferred from our data, we speculate that providers followed formal or informal algorithms of care that were relatively insensitive to serial cardiac marker testing once patients were hospitalized to "rule out myocardial infarction." Also, troponin testing may have influenced catheterization rates most in hospitals which adopted the test shortly after its introduction, and not in hospitals like ours which waited years before making the test available for clinical practice.[18] Of note, the true overall catheterization rate of 14% in this trial was lower than the base

Table 7. Outcomes at 60 Days

	CK (n=196)	CK and Troponin I (n=192)	Incidence Rate Ratio* (95% CI)	P Value
ED visits, median (range)	0 (0–2)	0 (0–4)	1.28 [0.80 to 2.05]	>.20
Hospitalizations, median (range)	0 (0–2)	0 (0–4)	1.54 [0.94 to 2.54]	.09
			Relative Risk* (95% CI)	
Diagnostic tests				
Echocardiograms	13 (7.4)	24 (13.4)	2.24 [1.11 to 4.69]	.02
Functional studies	13 (8.0)	22 (12.3)	1.67 [0.84 to 3.87]	.12
Procedures				
Catheterization	9 (5.1)	12 (6.7)	1.42 [0.56 to 3.87]	>.20
PCI	2 (1.1)	1 (0.6)	0.49 [0.21 to 2.80]	>.20
CABG	–	–	–	–
Medications				
Aspirin	148 (75.5)	143 (74.5)	1.00 [0.88 to 1.83]	>.20
Beta-blockers	102 (52.0)	105 (54.7)	1.05 [0.87 to 1.27]	>.20
Nitrates	90 (45.9)	80 (41.7)	0.92 [0.71 to 1.16]	>.20
Diuretics	113 (57.7)	96 (50.0)	0.88 [0.67 to 1.14]	>.20
ACE inhibitors	103 (52.6)	94 (49.0)	0.95 [0.76 to 1.89]	>.20
CA-channel blockers	72 (36.7)	72 (37.5)	1.02 [0.77 to 1.30]	>.20
Statins	84 (42.9)	86 (44.8)	1.04 [0.81 to 1.33]	>.20
Deaths	3 (1.7)	3 (1.6)	0.98 [0.21 to 4.87]	>.20

Adjusted for heart failure history and ED discharge using logistic regression; relative risks and confidence intervals estimated by nonparametric bootstrap resampling assuming baseline risk for hospitalized patients without heart failure undergoing CK testing alone. See Methods section for details. CK, creatine kinase; ED, emergency department; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; IQR, interquartile range; ICU, intensive care unit; ACE, angiotensin converting enzyme.

rate of 20% we used to calculate our sample size, and we could not exclude a 2-fold difference in this outcome. We incidentally noted a greater incidence of H2-blocker prescriptions on hospital discharge for CK-troponin patients, suggesting that low troponin values increased physicians' confidence that patients' symptoms were attributable to noncardiac causes. But we had not hypothesized this effect prior to the study, and it may represent a chance finding.

Patients who initially underwent troponin testing also underwent more echocardiography in a 60-day period following ED or hospital discharge, an effect that existed independent of early ED discharge and history of heart failure. This may also represent a chance finding, but could reflect an effort by physicians confronting normal CK and mildly elevated troponin levels to gather more information on an outpatient basis about patients' hearts after ACS has been excluded.

There were no other detectable long-term effects of testing; the marginally significant higher incidence of hospitalization for cardiovascular causes among the troponin group was explained by a single troponin-exposed patient hospitalized 4 times after VA discharge for complaints related to cocaine use.

This study has several limitations. First, it was a randomized trial of diagnostic test information rather than of clinical management. Information alone is often insufficient to change physician decisions and behavior, and a study that linked test information with guidelines for management might be a more effective way to improve resource use and health outcomes,[19] or at least to study the role of a diagnostic test in influencing those outcomes.[20] Troponin testing was not previously used at our study site, and physicians who may not have been familiar with its use may have been less sensitive to using troponin information in their clinical decisions. Most study physicians practiced at teaching hospitals where troponin was widely used, however, and all were aware it was a cardiac marker that provided information complementary to CK testing. Our study may have been undersized to detect a true effect of troponin testing on cardiac catheterization. In addition, troponin testing has been shown to be especially useful for stratifying patients into those who could benefit from interventions such as low–molecular weight heparin and GPIIa/IIIb inhibitors.[4–7] These were not widely available or used at the study hospital during the majority of this study, and it is possible that in settings where these are standard interventions, troponin could be shown to influence clinical care and outcomes in different or additional ways.

Discharge diagnoses were made based on all clinical information available to the study's inpatient physicians and were not independently verified. It is not possible using this approach to answer the question of whether the addition of troponin to CK testing decreased missed diagnoses of acute myocardial infarction, but biochemical data suggest the test increased sensitivity while decreasing specificity for detecting heart conditions, including acute myocardial infarction. Up to 40% of patients had troponin values in an "elevated non-AMI" category defined by the assay manufacturers, >90% of whom were given a diagnosis other than ACS (online-only Appendix). Troponin elevations in patients without ACS are most often attributable to nonischemic cardiovascular conditions and renal insufficiency, which delays clearance of the enzyme; we attribute most of the elevated non-AMI values in our study to nonischemic heart failure, renal insufficiency, hypertension, and/or assay measurement error in our initial (first-generation) troponin assay.[21] Elevated values in patients without ACS probably reflect subclinical myocardial damage and are predictive of worse cardiovascular prognosis regardless of troponin level or clinical diagnosis.[2,22]

Finally, the question of generalizability always accompanies a study of veterans, given substantial differences between VA and other health systems in patient population, hospital reimbursement, and health service organization. Though an overall late presentation after symptom onset highlights im-

portant differences between veterans and nonveteran populations typically represented in studies of ACS interventions, we nevertheless believe our study is generalizable to nonveteran populations for several reasons: the incidence of acute coronary syndromes was similar to that in other studies[10]; a substantial minority of patients in non-VA health systems present belatedly for evaluation[23]; and our ED-level findings remained significant even though differences in health systems, such as the lack of disincentives to admission in VA relative to non-VA settings, would have eliminated difference between groups if they were important. The prevalence of cocaine use is similar to values previously reported[24] and does not compromise generalizability of the study.

In summary, these findings support the dual use of CK and troponin testing as an effective technology for evaluating outpatient veterans who present belatedly with symptoms concerning for ACS. The data do not suggest that troponin testing can or should be used exclusively for triage decisions, or that nonelevated levels always predict safe patient discharges. Despite widespread acceptance of troponin testing as a criterion diagnostic standard, there remains a role for randomized trials to determine whether alone it is as effective an aid for ED triage decisions as CK testing with and without troponin, and whether troponin testing in inpatient settings can be shown to improve patient management with the adoption of guidelines linking management decisions to test results, or with the adoption of newer therapies indicated in the presence of abnormal cardiac enzyme levels.

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Supplementary Material

The following supplementary material is available for this article online:

Appendix. Definitions of Cardiac Marker Elevations.